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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-------------------------------------------------------------------------------------------|-------------|----------------------|---------------------|--------------------------|
| 10/784,528 | 02/23/2004 | Arthur M. Brown | 22884/04085 | 1521 |
| 24024 | 7590 | 03/17/2009 | EXAMINER | |
| CALFEE HALTER & GRISWOLD, LLP 800 SUPERIOR AVENUE SUITE 1400 CLEVELAND, OH 44114 | | | | SAJJADI, FEREYDOUN GHOTB |
| ART UNIT | | PAPER NUMBER | | |
| 1633 | | | | |
| | | | NOTIFICATION DATE | DELIVERY MODE |
| | | | 03/17/2009 | ELECTRONIC |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocket@calfee.com
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| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/784,528 | BROWN ET AL. | |
| | Examiner | Art Unit | |
| | FEREYDOUN G. SAJJADI | 1633 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 29 December 2008.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 4,7,8,15,26 and 27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 4,7,8,15,26 and 27 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) Notice of Informal Patent Application

6) Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 29, 2008 that includes a response to the advisory office action dated March 31, 2008, has been entered. Claim 4 has been amended and claim 6 cancelled. No claims were newly added. Accordingly, claims 4, 7, 8, 15, 26 and 27 are pending in the application and under current examination.

Applicants should note that newly canceled claim 6 is not compliant with 37CFR § 1.121 (c), because no claim text shall be presented for any claim in the claim listing with the status of “canceled”.

Response & Maintained Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 4, 6-8, 15, 26 and 27 stand rejected under 35 U.S.C. §112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. Applicants' cancellation of claim 6 renders its rejection moot. The rejection set forth on pp. 6-11 of the previous office action dated March 27, 2007, pp. 3-7 of the office action dated December 10, 2007, and the advisory action dated my 6, 2008 is maintained for claims 4, 7, 8, 15, 26 and 27 in part, for reasons of record.

As previously indicated, the specification is considered enabling for a method of inducing apoptosis in cultured cancer cell lines, comprising the step of introducing into said cells an expression vector comprising a nucleic acid encoding a human KChAP protein as set forth in SEQ ID NO: 2, said nucleic acid operably linked to a promoter active in cancer cell lines.

Applicants' amendment of base claim 4 to introduce the language wherein a promoter active in cancer cells is operably linked to the nucleotide sequence encoding human KChAP protein, while effectively addressing one ground of rejection, fails to overcome the remaining grounds for rejection.

Base claim 4 is directed to a method of inducing apoptosis in human prostate cancer cells or breast cancer cells in a tumor in a subject, following delivery of a viral vector expressing the human KChAP protein, by intratumoral injection. Therefore the claim broadly embraces a method of tumor cancer therapy.

As previously indicated, the heterotopic subcutaneous xenotransplantation of cell lines in an immunodeficient mouse fails to reflect human carcinoma. Additional issues relate to the use of cell lines (as opposed to primary tumor cells) and ectopic and heterotopic transplantation of said cell lines (versus orthotopic transplantation or primary tumor cells) in immunodeficient nude mice, as well as the paradox that enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation, especially in a tumor mass comprising a mixed cell population, bringing into question the validity of the claimed method as a therapeutic.

Applicants traverse the rejection, and argue that the Wands" factors analyzed by the Office actually may argue in favor of enablement, because the instant specification provides multiple working examples and very detailed and specific guidance, including KChAP overexpression in prostate cancer cells (example 1), inducing apoptosis in prostate cancer cells (example 2), inhibiting *in vivo* growth of subcutaneous implants of human prostate cancer cells (example 3), inducing apoptosis in breast cancer cells (example 4), and detection of cancer cells with anti-KChAP antibodies (example 5). Thus, one of ordinary skill in the art in a position to readily understand the full scope of the claimed invention and would only require routine, if potentially complex, experimentation to arrive at the full scope of the claimed invention.

Applicants' arguments have been fully considered, but are not found persuasive.

As previously indicated, the working examples embody a number of deficiencies that do not allow one of skill in the art to extrapolate their teachings to applications wherein a cancerous tumor may be treated in a subject. The evidence of record as a whole indicates that the heterotopic subcutaneous xenotransplantation of cell lines in an immunodeficient nude mouse fails to reflect human carcinoma, and therefore a person of skill in the art would need to carry out

further experimentation, with an uncertain outcome and constituting undue experimentation to introduce a viral expression vector encoding KChAP, to be effective in inducing apoptosis in human epithelial carcinoma *in vivo* or treating a subject with prostate or breast cancer. The prior art teachings of Kerbel et al., Vieweg et al. and Hoffman et al. were cited to demonstrate that orthotopically transplanted tumors do not necessarily recapitulate the ‘encouraging’ responses of their ectopically (usually subcutaneous) grown counterparts, and that the animal model exemplified in the instant specification, i.e. subcutaneously-growing human cell lines in immunodeficient mice, do not sufficiently represent clinical cancer, especially with regard to metastasis and drug sensitivity.

As a separate issue, Wang (Eur. J. Physiol. 448:274-286; 2004), states: “K⁺ channels favor tumor cell proliferation, therefore, inhibition of K⁺ channel function or down-regulation of K⁺ channel expression should inhibit tumorigenesis...On the other hand, K⁺ channels also promote apoptotic cell death...enhancement of K⁺ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation. This apparent paradox confounds the manipulation of K⁺ channel function and/or expression as an option for the treatment of cancers.” (pp. 281-282 bridging).

Thus, a person of skill in the art would need to engage in further experimentation to resolve the paradox outlined by Wang, whose outcome is unpredictable and thus constitutes further undue experimentation, especially since a tumor mass generally contains a heterogeneous population of cells at different stages of cancer progression.

Therefore the rejection is maintained for claims 4, 7, 8, 15, 26 and 27, for reasons of record and the preceding discussion.

Conclusion

Claims 4, 7, 8, 15, 26 and 27 are not allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action

after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Examiner, Art Unit 1633